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Title page

Positive coping styles and ACC volume - two related mechanisms for conferring resilience?

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Abstract

Stress exposure has been linked to increased rates of depression and anxiety in adults, particularly in females, and has been associated with maladaptive changes in the anterior cingulate cortex (ACC), which is an important brain structure involved in internalizing disorders. Coping styles are important mediators of the stress reaction by establishing homeostasis, and may thus confer resilience to stress-related psychopathology.

Anatomical scans were acquired in 181 healthy participants at age 25 years. Positive coping styles were determined using a self-report questionnaire (German Stress Coping Questionnaire, SVF78) at age 22 years. Adult anxiety and depression symptoms were assessed at ages 22, 23 and 25 years with the Young Adult Self-Report. Information on previous internalizing diagnoses was obtained by diagnostic interview (2-19 years).

Positive coping styles were associated with increased ACC volume. ACC volume and positive coping styles predicted anxiety and depression in a sex-dependent manner with increased positive coping and ACC volume being related to lower levels of psychopathology in females, but not in males. These results remained significant when controlled for previous internalizing diagnoses. These findings indicate that positive coping styles and ACC volume are two linked mechanisms, which may serve as protective factors against internalizing disorders.

Keywords: coping styles, perigenual anterior cingulate cortex, resilience, anxiety disorders, mood disorders

Word count: 3468

Introduction

Mood and anxiety disorders impose a serious burden in Western countries (WHO), with lifetime prevalences between 20.8% and 28.8%, respectively (Kessler *et al.*, 2005). Evidence suggests that women are more likely to develop these disorders through the lifespan (Kessler *et al.*, 2005; Mc Lean *et al.*, 2011). Among other causes, such as familial disposition, stress exposure has been related to increased rates of depression and anxiety (Levitan *et al.*, 2003). Therefore, coping styles, i.e. the way individuals try to restore the disturbed homeostasis in order to maintain well-being in stressful situations, may serve as a mediator between stress exposure and psychopathology, and may thus confer resilience (Feder *et al.*, 2009). Coping styles can be positive, i.e. stress-reducing, or negative, i.e., stress-enhancing (Wilkinson *et al.*, 2000; Erdmann and Janke, 2007; Heck *et al.*, 2009; Higgins and Endler, 1995). Indeed, depression and anxiety have been linked to less positive and more negative coping (Zhang *et al.*, 2009), making coping styles an attractive target for treatment intervention (Renaud *et al.*, 2014).

The role of the anterior cingulate cortex (ACC) in conferring risk for mood and anxiety disorders has long been recognized (Etkin and Wager, 2007; Drevets *et al.*, 2008). The ACC can be divided into five subregions: caudal, dorsal, rostral, perigenual and subgenual, with each of these parts covering distinct functions. While the more posterior parts of the ACC are mainly involved in cognitive processes such as error monitoring, the anterior parts cover emotional and social processes (Margulies *et al.*, 2007; Kelly *et al.*, 2009). For example, the perigenual ACC has been attributed a role in self-referential social processing (Amodio and Frith, 2006; Meyer-Lindenberg and Tost, 2012), while the subgenual part has been linked to emotion regulation (Meyer-Lindenberg and Tost, 2012), making these parts primary candidates for endophenotypes of

internalizing disorders. Accordingly, a lower volume in these regions has specifically been observed in patients with major depression and comorbid anxiety, suggesting a shared vulnerability pathway between the two disorders (van Tol *et al.*, 2010).

Notably, several studies have provided evidence for that the ACC is a convergence site of the effects of stress exposure (for a review see Holz *et al.*, 2015). In detail, a decreased ACC volume has been demonstrated following harsh corporal punishment lasting for at least three years (Tomoda *et al.*, 2009), following the attack on the World Trade Center on September 11th, 2001 (Ganzel *et al.*, 2008), and after exposure to cumulative adverse life events (Ansell *et al.*, 2012) as well as exposure to childhood adversity (Gerritsen *et al.*, 2012). Remarkably, during stress induction, the ACC has previously been associated with social-environmental risk factors acting in childhood, such as urban birth (Lederbogen *et al.*, 2011) and ethnic minority status (Akdeniz *et al.*, 2014), highlighting its importance in mediating the experience of psychosocial stress.

Using longitudinal data from an epidemiological cohort study of young adults followed since birth, the present investigation aimed to (i) examine the association between positive stress coping strategies and perigenual/subgenual ACC volume, (ii) explore the link between positive stress coping, and ACC volume and (iii) relate both to symptoms of anxiety and depression with a specific focus on sex-dependent effects (Kessler *et al.*, 2005; Mc Lean *et al.*, 2011).

Materials and Methods

Sample

This investigation was conducted in the framework of the Mannheim Study of Children at Risk, an ongoing epidemiological cohort study of the long-term outcome of early risk factors (for full details c.f. Laucht *et al.*, 2000). Infants were recruited from two obstetric and six children's hospitals in the Rhine-Neckar Region of Germany and were included consecutively into the sample according to a two-factorial design intended to enrich and to control the risk status of the sample [factor 1 varying the degree of obstetric complications, and factor 2 the degree of psychosocial adversity (for full details c.f. Laucht *et al.*, 1997; Laucht *et al.*, 2000)]. To control for confounding effects of family environment and infant medical status, only firstborn children with singleton births and German-speaking parents were enrolled. Assessments were conducted at the age of 3 months and at regular intervals throughout development (at the ages of 2, 4.5, 8, 11, 15, 19, 22, 23 and 25 years). Functional and structural magnetic resonance imaging was introduced in the most recent assessment at age 25 years. From the initial sample of 384 participants, 18 (4.7%) were excluded due to severe disabilities, and 57 (14.8%) were dropouts, leaving a final sample of 309 for the 25-year assessment. Of these, a subsample of N=182 right-handed individuals were selected to participate in an MRI session investigating brain volume. Exclusion criteria were the usual contraindications for MRI (such as heart pacemaker, neurological abnormalities, history of seizures, unconsciousness or head trauma), current psychiatric disorders as assessed by the Structured Clinical Interview for DSM-IV (SCID; American Psychiatric Association, 1994; German version, Wittchen *et al.*, 1997), and psychotropic medication. One participant was excluded due to systemic lupus erythematosus. The

study was approved by the ethics committee of the University of Heidelberg and written informed consent was obtained from all participants.

Assessments

Coping styles were assessed with the German Stress Coping Questionnaire (Stressverarbeitungsfragebogen SVF78; Janke *et al.*, 2002) at the participants' age of 22 years. The SVF78 consists of 13 subscales comprising either positive, i.e. stress-reducing, or negative, i.e. stress-enhancing coping styles. Here, we focus on positive coping styles, which consist of three broad dimensions encompassing devaluation/defense ("I tell myself that everything will turn out all right"), distraction ("I try to distract myself") and control ("I tell myself that I can cope with this"). A correlation matrix of these subcomponents is provided in Supplementary Table 1. Internal consistency and reliability have been reported to be fairly high [Cronbach's α = .77-.93; r = .74-.95 (split-half), r = .61-.74 (test-retest), respectively] and consistent construct validity and external validity have been confirmed (Ising *et al.*, 2001; Hampel *et al.*, 2002; Weyers *et al.*, 2005; Israelski, 2008). Data were missing for two participants, leaving a final sample of $N=179$ individuals.

Anxious and depressive behaviors during adulthood was assessed with the anxious/depressed subscale of the Young Adult Self-Report (YASR; Achenbach, 1991) at the participants' ages of 22 (range 0-26; mean 5.1; SD: 4.9), 23 (range 0-22; mean 4.3; SD: 4.4) and 25 years (range 0-23; mean 4.7; SD: 4.7). A composite score was computed by summing up the z-standardized scores across assessments. Data were missing for one subject. In addition, to ensure that the relationship between coping styles and ACC volume still exists for current anxiety and depression, we

reanalyzed the interactions with symptoms of anxiety and depression assessed at the age of 25 only.

Previous internalizing psychopathology (0=not present; 1= present) was assessed through diagnostic interviews with the parents (Mannheim Parent Interview; MPI Esser *et al.*, 1989) until the age of 11 years, and with the offspring at the age of 15 years using the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS-PL; Kaufman *et al.*, 1996; German version, Delmo *et al.*, 2000) and at the age of 19 years using the Structured Clinical Interview for DSM-IV (SCID; American Psychiatric Association, 1994; German version, Wittchen *et al.*, 1997).

Voxel-Based Morphometry (VBM) and statistical analysis

We acquired 1x1x1 mm T1-weighted anatomical images with 192 slices covering the whole brain (matrix 256x256, repetition time=2300ms, echo time=3.03ms, 50% distance factor, field of view 256x256x192mm, flip angle 9°) using a 3 T scanner (Magnetom TRIO, Siemens, Erlangen, Germany) with a standard 12-channel head coil. Images were bias-corrected and classified into gray matter, white matter, cerebrospinal fluid and non-brain tissue using Diffeomorphic Anatomical Registration through Exponentiated Lie algebra (DARTEL) registration toolbox (Ashburner, 2007). Data were segmented based on tissue probability maps, indexing the prior probability of any voxel in a registered image being gray or white matter or cerebrospinal fluid. An average template from the data was created, to which the images were registered. Additionally, the images were affine-transformed to MNI space and smoothed with a 6-mm FWHM kernel. Total intracranial volume was calculated by adding the tissue probabilities of gray matter, white matter and cerebrospinal fluid and used as a covariate. For group statistics of

gray matter images, coping style was entered as a covariate of interest while additionally controlling for total intracranial volume and sex. To test our a priori hypothesis, anatomical region of interest (ROI) masks comprising the bilateral ACC were derived from the WFU PickAtlas v2.4 (Maldjian *et al.*, 2003), where family-wise error (FWE) correction was applied with a threshold of $p < .05$. Additionally, exploratory whole brain analyses were performed with a $p < .001$ uncorrected threshold and a criterion of 10 adjacent voxels. For display purposes, the statistical threshold was set at $p = .005$ uncorrected in the ROI. To visualize and further analyse the effects using regression analysis (i.e., ACC by sex on depression/anxiety) and mediation analysis using the Sobel Test (Baron and Kenny, 1986), mean contrast values of each participant were extracted from the FWE-corrected significant cluster (45 voxel) and exported to SPSS Statistics 20 (IBM, Armonk, NY).

Results

Sample characteristics

As expected, females exhibited increased YASR anxiety and depression scores and were more likely to have a history of previous internalizing psychopathology at a trend level (Table 1).

While no sex difference emerged with regard to positive coping styles in general, females made use of more distraction compared to males.

VBM

Positive coping styles were associated with increased volume in the perigenual ACC extending to the subgenual part ($t(175)=4.22$, $p_{FWE}=.007$; Figure 1). After exclusion of outliers, the results remained significant ($t(173)=3.92$, $p_{FWE}=.02$). Whole brain results are depicted in Supplementary Table 2. When controlling for previous psychopathology, the results remained unchanged ($t(174)=4.19$; $p_{FWE}=.007$). When parsing positive coping styles into its subcomponents, positive self-instruction ($t(175)=4.31$, $p_{FWE}=.009$) was the strongest predictor of ACC volume, followed by denial of guilt ($t(175)=3.96$, $p_{FWE}=.02$), distraction ($t(175)=3.65$, $p_{FWE}=.04$) and reaction control ($t(175)=3.67$, $p_{FWE}=.04$). The overlap between these effects is shown in Figure 2. In a second step, we tested for a possible interaction with sex on ACC volume, which reached significance only at an uncorrected level (positive coping styles by sex: $t(172)=3.03$, $p_{uncorrected}=.001$).

Figure 1

Figure 2

Association with anxiety and depression

A significant interaction effect of positive coping styles with sex and of ACC volume with sex on the composite score of anxiety/depression during adulthood (covering age 22-25 years) was obtained ($\beta = -.33$, $p = .02$; $\beta = -11.68$, $p = .03$; respectively; Figure 3). In detail, positive coping styles and increasing ACC volume were associated with decreasing anxiety and depression in females ($\beta = -.29$, $p = .01$; $\beta = -11.02$, $p = .01$, respectively), while no such pattern was observed in males ($\beta = .03$, $p = .64$; $\beta = .66$, $p = .80$, respectively). The results remained unchanged when controlled for previous internalizing psychopathology. Further, results remained significant when outliers were excluded. In a further step, we examined a mediating effect of ACC volume on the relationship between positive coping and anxiety in females, which yielded a significant indirect effect ($p = .047$) with a significant path between positive coping and ACC volume ($\beta = .006$, $p = .02$), and between ACC volume and anxiety and depression ($\beta = -8.95$, $p = .04$). Moreover, the direct path between positive coping and anxiety remained significant, albeit at a lower threshold ($\beta = -.24$, $p = .04$), suggesting partial mediation. The results were similar when the outcome was current anxiety/depression at the age of 25 years (positive coping style by sex: $\beta = -.51$, $p = .038$; ACC volume by sex: $\beta = -19.47$, $p = .036$; mediation analysis: $p = .05$).

Positive self-instruction was the subcomponent which was the strongest predictor of ACC volume and of positive coping styles ($r = .79$, $p < .001$). Likewise the interaction effect of positive self-instruction with sex on depression/anxiety was significant ($\beta = -.29$, $p < .001$), indicating a significant inverse association between positive coping styles and anxiety/depression in females

($\beta = -.34$, $p < .001$) but, again, not in males ($p = .34$). The same was true for the interaction between sex and denial of guilt ($\beta = -.21$, $p = .03$), but not for distraction ($p = .22$) or reaction control ($p = .72$).

Figure 3 about here

Discussion

The present study investigated the association of coping styles with ACC volume and internalizing symptoms. Our findings from a prospective study over 25 years indicate that positive coping styles are associated with increased ACC volume. Both ACC volume and positive coping styles predicted symptoms of anxiety and depression in a sex-dependent manner, with inverse relationships emerging in females only.

Positive coping styles were associated with increased ACC volume, specifically with the perigenual extending to the subgenual part. This region is linked with social processing, the regulation of negative emotions and extinction learning (Etkin *et al.*, 2011; Meyer-Lindenberg and Tost, 2012), thus supporting a potential role in conferring risk and resilience to stress-related disorders such as depression and anxiety. Interestingly, greater extinction memory has been associated with an increased thickness of the ventral medial prefrontal cortex (Milad *et al.*, 2005), which is adjacent to the pACC, indicating that the size of this region might be directly related to the ability to modulate fear. Notably, activity in the pregenual ACC during attention interference in individuals at high familial risk has been suggested to play a role in assigning resilience to anxiety and depression (Peterson *et al.*, 2014). Further, a twin study of combat-exposed subjects showed that a decreased gray matter volume in the ACC is unique to those who develop PTSD when compared to their non-affected twins (exposed and non-exposed and their co-twins), suggesting that the reduction may not be a possible familial vulnerability factor (Kasai *et al.*, 2008). Previous studies investigating social evaluative stress processing have emphasized the vulnerability of this region to environmental stressors, including urbanicity (Lederbogen *et al.*, 2011) and migration (Akdeniz *et al.*, 2014). Moreover, it has been demonstrated that low

subjective social status covaries with reduced gray matter volume in the pACC (Gianaros *et al.*, 2007). Interestingly, the pACC is one of the key regions involved in the regulation of the HPA axis (Diorio *et al.*, 1993), including the cortisol awakening response (Boehringer *et al.*, 2015), thus providing a plausible biological mechanism linking susceptibility to stress with the ACC. Thus, a decreased volume and cortical thickness in the ACC along with increased activity during stress processing and a blunted response during attention interference might serve as risk endophenotypes of psychopathology. In sum, the risk and resilience trajectories of the ACC might point to adaptive emotional, behavioral and physiological response of this region to environmental and psychosocial stressors, and may thus represent an interesting target for intervention to reduce allostatic load. However, it is noteworthy that the pACC is tightly connected to other corticolimbic areas, including the amygdala and hippocampus, and is therefore unlikely to promote complex neurobehavioral processes independently.

Interestingly, while we observed a direct association of positive coping styles and ACC volume, an interaction with gender emerged when considering internalizing psychopathology. Females exhibited increased anxiety/depression symptoms in this sample, which echoes previous reports (Kessler *et al.*, 2005; Mc Lean *et al.*, 2011). Therefore, it seems plausible that protective factors such as increased positive coping styles, and thereby ACC volume, only emerge when exceeding a specific psychopathological level or, in other words, only when homeostasis is disturbed and stress-reducing mechanisms are needed to restore allostatic load. Consequently, it might be the case that studies in clinical samples with a higher stress load across both sexes may not replicate a gender dependent effect but may rather confirm effects of positive coping styles and ACC volume on psychopathology for both genders.

A related concept to positive coping styles is reappraisal, which is defined as interpreting a potentially emotion-eliciting situation in a way that changes its emotional impact (Gross and John, 2003) either by reappraisal of stimuli in a positive way or reappraisal via perspective-taking (detached observer), both of which are widely used in emotion regulation tasks. So far, there have been several neuroimaging studies investigating the neural underpinnings of reappraisal.

According to a recent meta-analysis, reappraisal in general has been related to activation in the semantic system including the inferior prefrontal gyrus, while reappraisal of stimuli additionally activated the dorsal attention system (medial prefrontal cortex and dorsal prefrontal cortex) (Messina *et al.*, 2015). Interestingly, there is also evidence that increased dispositional cognitive reappraisal showed a higher activation of the right vmPFC and the lateral OFC over the course of symptom provocation in dental phobic individuals (Hermann *et al.*, 2013). Consistent with these functional differences, cognitive reappraisal has been related to an increased volume in the dorsal region of the ACC (Giuliani *et al.*, 2011) as well as to an increased ventromedial prefrontal cortex volume [(Welborn *et al.*, 2009); but see Hermann, *et al.* (2014)], the latter result partially overlapping with the outcome of the present study. Indeed, in analogy with findings showing that positive coping styles are important mediators between stress and resilience to depression and anxiety (Roohafza *et al.*, 2014; Ren *et al.*, 2015), there is also evidence that individuals using cognitive reappraisal exhibit less depressive symptoms (Cutuli, 2014).

In contrast to positive reappraisal, positive coping styles cover a rather broad range of stress reducing strategies, which involve two mechanisms of executive functioning recruitment. On the one hand, positive coping encompasses cognitive mechanisms such as positive self-instruction,

which partly overlap with cognitive reappraisal, and, on the other hand, response modifications such as reaction control. While the first targets antecedent-focused strategies, i.e. the modification of the emotional stimuli before the emotional response, the latter is more a response-focused strategy, activated during the emotional response to a stimulus (Cutuli, 2014). Neuroimaging studies on positive coping styles have been rather sparse. Considering response modification mechanisms, Hermann et al., (2014), found expressive suppression to be negatively related to neuroticism and positively associated with dorsomedial and ventromedial PFC gray matter volume, with the latter overlapping with the present results. In sum, while functional data implicate more dorsal parts of the ACC in reappraisal, volume in the ventromedial part of the ACC seems to be a central mediator of both cognitive reappraisal and expressive suppression. This is in line with our results given that positive self-instruction, a subcomponent of cognitive reappraisal, and reaction control, a strategy of expressive suppression, are both predictors of pACC volume.

The acquisition of positive coping styles is a central aspect of cognitive behavioral therapy (CBT). Coping skills acquired during CBT and their independent implementation were found to predict the risk of relapse in the year following treatment termination in depressive individuals (Strunk *et al.*, 2007). Similarly, mastery of active problem-focused coping strategies immediately after completion of therapy predicted better psychopathological and social outcome 12–18 months following CBT in schizophrenia (Andres *et al.*, 2003). Likewise, symptom improvement after CBT was attributed to coping and the ability to reappraise misinterpretations rather than to clinical insight, duration of illness, gender or neuropsychological function (Premkumar *et al.*, 2011), underlining the importance of this key therapeutic component. According to our results,

the ability to attribute oneself with the capability and competence to control a stressor might be one of the most important aspects of positive coping strategies, followed by the degradation and the reappraisal of the stressor. Interestingly, apart from coping styles, ACC volume also seems to be critically involved in effective CBT. Evidence exists that CBT alters ACC activity to threat (Lipka *et al.*, 2014) and ACC volume predicts treatment response (Bryant *et al.*, 2008) and symptom improvement (Fujino *et al.*, 2015) after CBT.

Our study should be considered in light of some limitations. First, coping styles were assessed prior to ACC volume, which does not allow us to make a definitive statement on the direction of the relationships. Both possibilities may be conceivable, i.e., that a positive coping style may increase ACC volume by decreasing stress-dependent atrophy, but also that positive coping styles arise due to an increased volume in the ACC possibly promoting a better capacity to regulate emotions. Second, functional data of the pACC during stress processing are not available. One candidate paradigm to address this may be the Montreal Imaging Stress Task (Lederbogen *et al.*, 2011; Akdeniz *et al.*, 2014), in which the stress-buffering effect of positive coping styles could be directly examined. Third, the multi-dimensional, dynamic nature of the resilience construct (Luthar *et al.*, 2000) cannot be tested in our currently healthy sample given the lack of a group with a clinically significant level of depression or anxiety. The term resilience as used throughout the paper is therefore more reflective of a general protective factor (Luthar *et al.*, 2000), i.e. an individual's capacity to cope positively with stressful situations. Future studies are needed to test the promotion of resilience by positive coping skills using designs which include stressor-exposed individuals who develop a disease versus those who do not and/or, most elegantly, patients and their non-exposed twins.

Conclusion

In conclusion, increased ACC volume and positive coping styles are two linked mechanisms, which may represent possible protective factors for internalizing disorders. Since coping mechanisms can be modified, with our results underlining positive self-instruction as the most important strategy to control stressors, this may offer a more specific target for cognitive behavioral therapy to promote positive adaptation within the context of significant adversity.

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Conflicts of interest

TB served in an advisory or consultancy role for Hexal Pharma, Lilly, Medice, Novartis, Otsuka, Oxford outcomes, PCM scientific, Shire and Viforpharma. He received conference attendance support and conference support or received speaker's fees from Lilly, Medice, Novartis and Shire. He is/has been involved in clinical trials conducted by Lilly, Shire & Viforpharma. AML received consultancy fees from Lundbeck International Neuroscience, Thieme Verlag Germany and Elsevier USA; for lectures including travel fees from Aula Médica Congressos, Grupo Ferrer International, Janssen-Cilag, Lilly Deutschland, Roche Pharma AG; and also grants from the Federal Office for Radiation Protection Germany and the Prix Roger de Spoelberch. All other authors declare that they have no biomedical financial interest or potential conflicts of interest. The present work is unrelated to the above grants and relationships.

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Table 1. Sample characteristics by sex

<i>Sex</i>	<i>Males</i>	<i>Females</i>	<i>p-value</i>
No. (%)	75 (41.44)	106 (58.56)	
YASR Anxiety and Depression, mean (SD) ^a	-1.12 (1.98)	.25 (2.81)	<.001 ^b
Previous internalizing psychopathology, No. (%)	17 (22.67)	38 (35.85)	.06 ^c
Overall Positive Coping Styles, mean (SD)	12.81 (3.23)	13.26 (2.40)	.28 ^b
Positive Self-Instruction mean (SD) ^d	16.41 (5.05)	16.58 (3.86)	.79 ^b
Denial of Guilt, mean (SD) ^d	11.27 (4.35)	11.22 (3.32)	.93 ^b
Distraction, mean (SD) ^d	11.23 (4.68)	13.18 (3.83)	.003 ^b
Reaction Control, mean (SD) ^d	14.64 (4.46)	15.30 (3.41)	.26 ^b

Note: ^a sum of z-standardized values from age 22 years - 25 years; ^b t-test; ^c X²-test; ^d subcomponent of positive coping styles; raw values for the different scales are presented

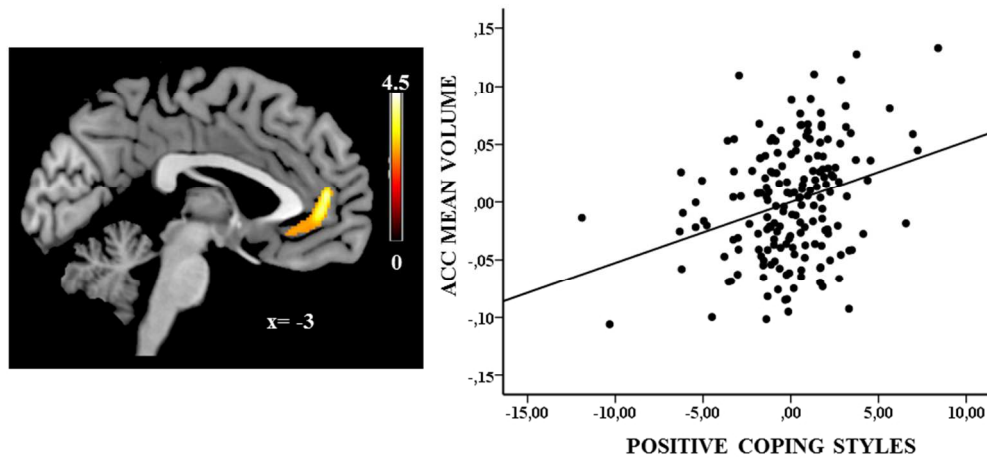
Figure captions

Figure 1. Association between positive coping styles and ACC volume (peak -3 48 9, $p_{FWE}=.01$).

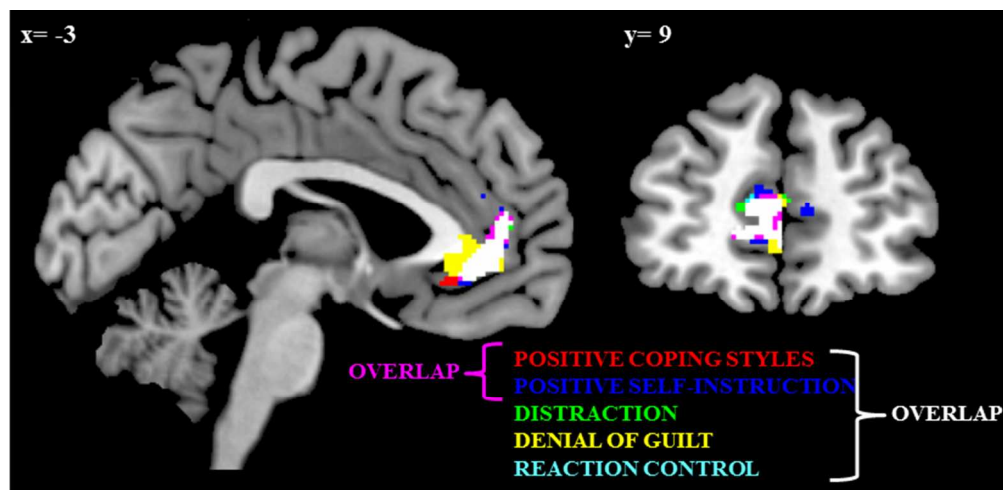
The association remained significant when outliers were excluded ($p_{FWE}=.02$). Note that the scatter plot is adjusted for confounders and therefore negative levels of positive coping styles emerge.

Figure 2. Associations of different positive coping styles with ACC volume are overlaid, with their overlapping part in white.

Figure 3. Interaction effect of positive coping styles with sex (A, $p=.02$) and of ACC volume with sex (B; $p=.03$) on YASR anxiety and depression.

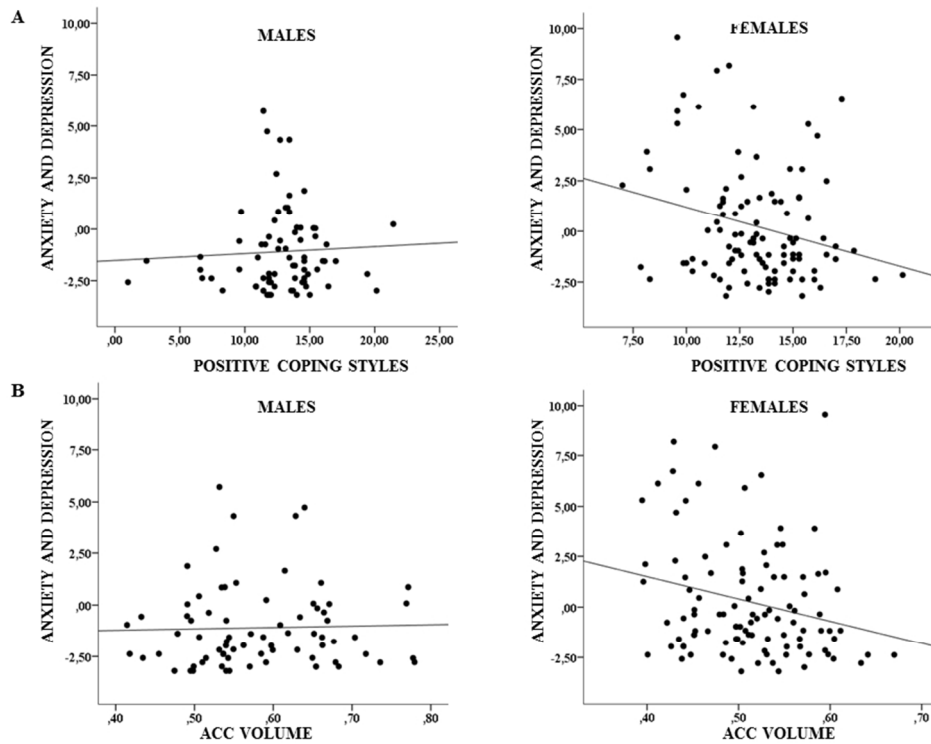


Association between positive coping styles and ACC volume (peak -3 48 9, $p_{FWE}=.01$). The association remained significant when outliers were excluded ($p_{FWE}=.02$). Note that the scatter plot is adjusted for confounders and therefore negative levels of positive coping styles emerge.
253x118mm (96 x 96 DPI)



Associations of different positive coping styles with ACC volume are overlaid, with their overlapping part in white.

217x105mm (96 x 96 DPI)



Interaction effect of positive coping styles with sex (A, $p=.02$) and of ACC volume with sex (B; $p=.03$) on YASR anxiety and depression.
254x190mm (96 x 96 DPI)